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Reactions of Acyl-aminoquinone Tosylhydrazones. III.[1] A Simple Synthesis of 7-Substituted Pyrrolo[1,2-*a*]-indoloquinones and Related Compounds

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Thermolysis of 2-acetyl-3,6-diamino-5-methyl-1,4-benzoquinone tosylhydrazones (**2a**—**c**) prepared by the reactions of monoaminoquinone tosylhydrazones (**1a**—**c**) with the corresponding amines gave 5-hydroxyindoloquinones (**5a, b**) and related compounds. In the case of 2-acetyl-5-methyl-6-morpholino-3-pyrrolidino-1,4-benzoquinone tosylhydrazone (**2e**), 7-morpholino- (**4e**) and 7-hydroxypyrrolo[1,2-*a*]indoloquinone (**5a**) were obtained.

The mechanism of this reaction, which afforded new indoloquinone ring systems, was investigated.

Keywords——tosylhydrazones; thermolysis; aminoindoloquinones; hydroxyindoloquinones; indazoloquinones

In the previous communication,[3] we reported that the thermolysis of acyl-monoaminoquinone tosylhydrazones (**1a**—**c**) gave pyrrolo[1,2-*a*]indoloquinones and analogous products (**3a**—**c**) in a one-step reaction. For the simple syntheses of 7-substituted pyrrolo[1,2-*a*]indoloquinones and related compounds, we examined the thermolysis of diaminoquinones (**2a**—**e**) and attempted to elucidate the mechanism to account for these observations.

2a—**c**[1] were obtained in ca. 40% yields by the reactions of monoaminoquinones (**1a**—**c**) with excess amines (pyrrolidine, piperidine, and morpholine) at −10° in chroloform for 48 hr. **2a** gave 7-hydroxypyrrolo[1,2-*a*]indoloquinone (**5a**) (12%), 1-tosyl-5-pyrrolidinoindazole (**6a**) (17%), and 5-pyrrolidinoindazole (**7a**) (49%) when it was heated at its decomposition point. All physical constants of **5a** were identical with those of the authentic sample.[4] Similarly, **2b** gave **5b** and **7b**. It is interesting that **2c** did not give **5c** but formed **7c** and a small amount of N-tosylmorpholine, same as in the case of monomorpholinoquinone[3] (**1c**). A small amount of ditolyl disulfide and ditolyl thiolsulfonate were isolated in all these thermolysis reactions. The structures of indazoloquinones (**6a**) and (**7a**—**c**) were confirmed by comparison with the authentic samples.[1]

As the indazoloquinones thus obtained have chromophors common to rifamycin derivatives[5] and mitomycins in their structures, they may be expected to have interesting biological actions.

Since **6a**—**c** and **8a** are formed from **2a**—**c** and then converted into **8b** in the acid-catalyzed reactions,[1] it is clear that the 5-position of indazoloquinone is easily attacked by nucleophilic reagents. Similarly, the 7-position of pyrroloindoloquinone may be attacked by nucleophiles. Therefore, it is considered that 7-hydroxy derivatives (**5a, b**) will be formed *via* **4a, b** by pyrolysis reaction of **2a, b**. In order to obtain **4**, at first, the relative rates of the intra- or inter-molecular nucleophilic substitution reactions of **1a**—**c** and **2a**—**c** with hydrogen ion were examined by means of changes in ultraviolet (UV) spectra with time and thin–

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[1] Part II: M. Akiba, Y. Kosugi, and T. Takada, *Chem. Pharm. Bull.* (Tokyo), **24**, 1731 (1976).
[2] Location: *1432-1, Horinouchi, Hachioji, Tokyo, 192-03, Japan.*
[3] T. Takada, Y. Kosugi, and M. Akiba, *Tetrahedron Letters*, **1974**, 3283.
[4] T. Takada and M. Akiba, *Chem. Pharm. Bull.* (Tokyo), **20**, 1785 (1972).
[5] A.N. Tischler, F.M. Tompson, L.J. Libertini, and M. Calvin, *J. Med. Chem.*, **17**, 948 (1974).

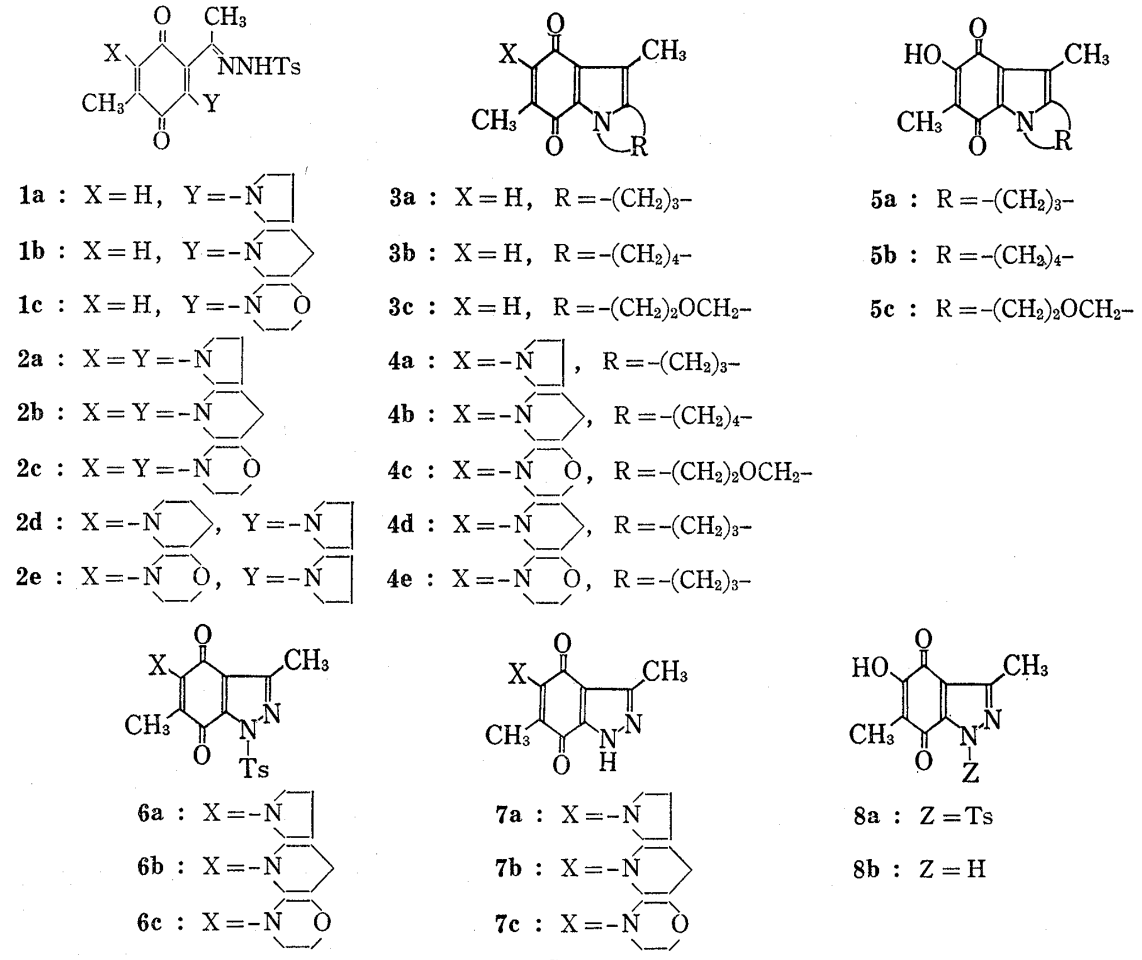

Chart 1

layer chromatography (TLC). As a result, it became clear that those of **1a**—**c** and **2a**—**c** with various amino groups decreased in the order of, pyrrolidino, piperidino, and morpholino groups.[1] Consequently **2d**, **e** were prepared from **1a** by their reaction with piperidine and morpholine. (Substitution reactions with amines[6] did not occur and **1b**, **c** were not obtained). As expected, by the pyrolysis reaction, **2e** gave **4e** (35%) besides **5a** (8%) and **7c** (34%). **2d** did not give **4d**. On treatment with 1% hydrochloric acid, **4e** gave **5a** in a quantitative yield. Table I shows the results of the pyrolysis reactions.

To explain the above results, we propose such a mechanism that decomposition of acetylmono- (**1**) and di-aminoquinone tosylhydrazone (**2**) gives carbene intermediate, which undergoes further insertion and presumably intermolecular disproportionation to form indoloquinone (**3** and **4**), and indazoloquinone (**6**) as shown in Chart 2.

TABLE I. Thermolysis of Diaminoquinones (**2**)

Compd. No.	Yield of product (%)			
	4	**5**	**6**	**7**
2a	—	12.4	17.1	49.1
2b	—	14.4	—	13.5
2c	—	—	—	38.5
2d	—	23.0	trace	31.8
2e	34.8	8.5	—	33.9

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[6] M. Akiba, N. Yamamoto, Y. Kosugi, and T. Takada, unpublished.

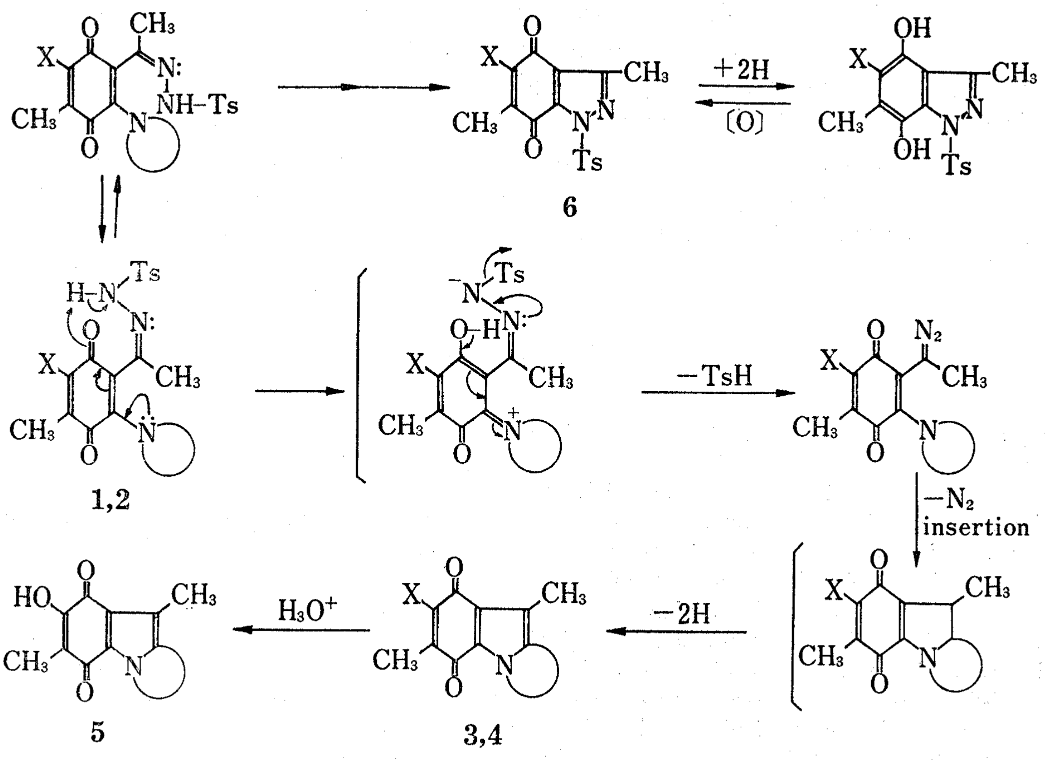
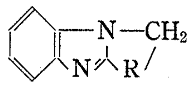


Chart 2

In the insertion reaction of carbene, the formation of a transition state containing a 6-membered ring as an intermediate has been assumed. Suschitzky, *et al.*[7] have reported the synthesis of **9** and **10** by the thermolysis of *o*-substituted phenyl-2- or 4-substituted 3-pyridyl azides, and that the yield increased with the variation of R from -$(CH_2)_2$- to -$(CH_2)_3$-, -$(CH_2)_4$-, and -CH_2O-CH_2-. Recently, Ban, *et al.*[8] reported a similar example.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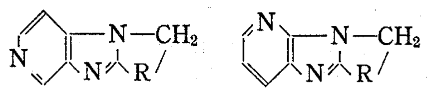
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Though the results of the thermolysis of acyl-monoaminoquinone tosylhydrazones, as previously reported,[3] show quite a reverse tendency, it may be explained by assuming that the carbene formation is influenced by the amino groups and its ease decreased in the order of pyrrolidino, piperidino, and morpholino group. This is also in accordance with the order of the relative rates of the indazoloquinone formation in the acid-catalyzed intramolecular cyclization reaction of mono- (**1**) and di-aminoquinone (**2**).[1] On the other hand, yields of indoloquinones from diaminoquinones (**2**) increased from **2a** to **2d** and **2e**. This is easily explained by assuming that the electron-donating effect of CH_3 is influenced by the adjacent amino group.

The fact that ditolyl disulfide, ditolyl thiolsulfonate, toluenesulfonic acid, and water originating from toluenesulfinic acid[9] are obtained suggests the formation of the carbene as an intermediate. It is considered that this water formed as a by-product acts as a nucleophilic reagent in the intermolecular substitution reaction. The mechanism of the indazolo-

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[7] O.M. Cohn, R.K. Smalley, and H. Suschitzky, *J. Chem. Soc.*, **1963**, 1666.

[8] Y. Ban, H. Kimura, and T. Oishi, Abstracts of the 7th Congress of Heterocyclic Chemistry, Chiba, Japan, 1974, p. 205.

[9] *a*) L. Horner and O.H. Basedow, *Ann. Chem.*, **612**, 108 (1958); *b*) L. Bauer and J. Cymerman, *J. Chem. Soc.*, **1950**, 109.

quinone formation in the pyrolysis reaction may be explained in the same way as those in the acid-catalyzed nucleophilic substitution reaction,[1] as shown in Chart 2.

As mentioned above, we have succeeded in the synthesis of 7-hydroxypyrrolo[1,2-*a*]-indoloquinones and related compounds by the method based on a new idea quite different from the conventional one. we believe that this thermal decomposition reaction may be of great utility in the simple synthesis of 1,2-disubstituted indoloquinones, and studies are now under way for the improvement of this reaction and further approach to the total synthesis of mitomycins.

Experimental

All melting points were measured on a Yanagimoto Micro-melting Point Apparatus, and are uncorrected. NMR spectra were taken on a JEOL PS-100 at 100 MHz, using tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi Model RMU-7L.

General Procedure for the Preparation of 2-Acetyl-3,6-diamino-5-methyl-1,4-benzoquinone Tosylhydrazones (2)——To a solution of 500 mg of the corresponding monoaminoquinone (**1**) in 30—50 ml of $CHCl_3$, 1 g of the amine (pyrrolidine, piperidine, or morpholine) in 10 ml of $CHCl_3$ was added, the mixture was stirred for 10 min and then allowed to stand overnight at room temperature. $CHCl_3$ was evaporated *in vacuo* at below 30° and the resulting residue was purified through silica gel or alumina column chromatography. Reliable combustion analysis could not be obtained owing to the instability of the title compounds.

2-Acetyl-5-methyl-6-piperidino-3-pyrrolidino-1,4-benzoquinone Tosylhydrazone (2d)——The title compound was prepared in 88.5% isolated yield by the general procedure. Characteristic properties of **2d** follow: mp 161° (decomp.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3205 (NH), 1628, 1595, 1535 (N–C=C–C=O), 1160 (SO_2). NMR ($CDCl_3$) δ: 7.80 (2H, d, $J=8$ Hz, aromatic proton), 7.25 (2H, d, $J=8$ Hz, aromatic proton), 3.15—3.50 (8H, m, CH_2), 4.21 (3H, s, CH_3), 2.03 (3H, s, CH_3), 1.90 (3H, s, CH_3), 1.50—1.80 (10H, m, CH_2).

2-Acetyl-5-methyl-6-morpholino-3-pyrrolidino-1,4-benzoquinone Tosylhydrazone (2e)——The title compound was prepared in 55.3% isolated yield by the general procedure. Characteristic properties of **2e** follow: mp 170—171° (decomp.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3190 (NH), 1623, 1583, 1530 (N–C=C–C=O), 1158 (SO_2).

Thermolysis of 2-Acetyl-5-methyl-3,6-dipyrrolidino-1,4-benzoquinone Tosylhydrazone (2a). Formation of Ditolyl Disulfide, Ditolyl Thiolsulfonate, 2,3-Dihydro-7-hydroxy-6,9-dimethyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]-indole (5a), 3,6-Dimethyl-4,7-dioxo-5-pyrrolidino-1-tosyl-1*H*-indazole (6a), and 3,6-Dimethyl-4,7-dioxo-5-pyrrolidino-1*H*-indazole (7a)——50 mg of dipyrrolidinoquinone tosylhydrazone (**2a**) was heated at 180° in an oil bath for a few minutes, at which time all starting material had been consumed (TLC, silica gel). Upon cooling, the reaction mixture was purified by column chromatography over silica gel using C_6H_6–$CHCl_3$. 5 mg (12.4%) of 7-hydroxypyrroloindole (**5a**), 7 mg (17.1%) of 1-tosylindazole (**6a**), and 13 mg (49.1%) of indazole (**7a**) were isolated. **5a** obtained here was identical in all respects with that prepared previously. TLC and GLC analysis of the reaction mixture showed the presence of ditolyl disulfide and ditolyl thiolsulfonate. Characteristic properties of these compounds follow: 7-Hydroxypyrroloindole (**5a**): Recrystallization from *n*-hexane gave red needles, mp 189—192°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3330 (OH), 1635 (C=O), 1483, 1328, 1100, 738. NMR ($CDCl_3$) δ: 7.33 (1H, s, OH), 4.20 (2H, t, $J=7.5$ Hz, $NC\underline{H}_2CH_2$), 2.43—2.86 (4H, m, $-CH_2-CH_2-$), 2.25 (3H, s, CH_3), 1.95 (3H, s, CH_3). Mass Spectrum *m/e*: 231 (M^+). 1-Tosylindazole (**6a**): Reliable combustion analysis could not be obtained owing to the instability of this compound. mp 154—156° (decomp.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1680 (C=O), 1620 (C=O), 1520 (N–C=C–C=O), 1390, 1280, 1180 (SO_2), 920, 660. NMR ($CDCl_3$) δ: 8.21 (2H, d, $J=8$ Hz, aromatic proton), 7.27 (2H, d, $J=8$ Hz, aromatic proton), 3.73 (4H, m, $-CH_2NCH_2-$), 2.53 (3H, s, CH_3), 2.45 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.93 (4H, m, $-CH_2CH_2-$). Indazole (**7a**): Recrystallization from *n*-hexane gave red-brown solid, mp 185—190°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3100 (NH), 1665 (C=O), 1580 (N–C=C–C=O), 1480, 1435, 1365, 1280, 1260, 1060, 860. NMR ($CDCl_3$) δ: 3.80 (4H, m, $-CH_2NCH_2-$), 2.62 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.92 (4H, m, $-CH_2CH_2-$). Mass Spectrum *m/e*: 245 (M^+).

Thermolysis of 2-Acetyl-5-methyl-3,6-dipiperidino-1,4-benzoquinone Tosylhydrazone (2b). Formation of Ditolyl Disulfide, Ditolyl Thiolsulfonate, 1,2,3,4-Tetrahydro-8-hydroxy-7,10-dimethyl-6,9-dioxopyrido[1,2-*a*]-indole (5b), and 3,6-Dimethyl-4,7-dioxo-5-piperidino-1*H*-indazole (7b)——100 mg of dipiperidinoquinone tosylhydrazone (**2b**) was heated at 190° in an oil bath for a few minutes. Upon cooling, the reaction mixture was treated in the same way as described above. 7.1 mg of pyridoindole (**5b**) and 7 mg of indazole (**7b**) were isolated respectively. TLC and GLC analysis of the reaction mixture showed the presence of ditolyl disulfide and ditolyl thiolsulfonate. Characteristic properties of these compounds follow. 8-Hydroxypyridoindole (**5b**): Recrystallization from *n*-hexane gave red needles, mp 212—214°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3325 (OH), 2925, 1635 (C=O), 1325, 1093, 735. Mass Spectrum *m/e*: 245 (M^+). Indazole (**7b**): Recrystallization from *n*-hexane gave dark red solid, mp 155—160°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3100—3200 (NH), 1660 (C=O), 1635 (C=O), 1545 (N–C=C–C=O), 1290, 1080, 945. NMR ($CDCl_3$) δ: 10.60 (1H, broad, NH), 3.36 (4H, m, $-CH_2NCH_2-$), 2.67 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.70 (6H, m, $-(CH_2)_3-$). Mass Spectrum *m/e*: 259 (M^+).

Thermolysis of 2-Acetyl-5-methyl-3,6-dimorpholino-1,4-benzoquinone Tosylhydrazone (2c). Formation of N-Tosylmorpholine, Ditolyl Disulfide, Ditolyl Thiolsulfonate, and 3,6-Dimethyl-5-morpholino-4,7-dioxo-1*H*-indazole (7c)——50 mg of dimorpholinoquinone tosylhydrazone (**2c**) was heated at 210° in an oil bath for a few minutes. Upon cooling, the reaction mixture was treated in the same way as described above. 3 mg of N-tosylmorpholine and 10 mg of indazole (**7c**) were isolated. TLC analysis of the reaction mixture showed the presence of ditolyl disulfide and ditolyl thiolsulfonate. Characteristic properties of **7c** follow. Recrystallization from *n*-hexane gave brown-red solid, mp 215—220°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3200 (NH), 1663 (C=O), 1620 (C=O), 1550 (N–C=C–C=O), 1450, 1233, 1110, 955, 750. NMR ($CDCl_3$) δ: 3.85 (4H, t, $J=5$ Hz, CH_2), 3.42 (4H, t, $J=5$ Hz, CH_2), 2.68 (3H, s, CH_3), 2.07 (3H, s, CH_3). Mass Spectrum *m/e*: 261 (M^+).

Thermolysis of 2-Acetyl-5-methyl-6-piperidino-3-pyrrolidino-1,4-benzoquinone Tosylhydrazone (2d). Formation of Ditolyl Disulfide, Ditolyl Thiolsulfonate, 2,3-Dihydro-7-hydroxy-6,9-dimethyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (5a), 3,6-Dimethyl-4,7-dioxo-5-piperidino-1-tosyl-1*H*-indazole (6b), and 3,6-Dimethyl-4,7-dioxo-5-piperidino-1*H*-indazole (7b)——50 mg of diaminoquinone tosylhydrazone (**2d**) was heated at 180° in an oil bath for a few minutes, at which time all the starting material had been consumed. Upon cooling, the reaction mixture was treated in the same way as described previously. 5.5 mg (23.0%) of pyrroloindole (**5a**) and 8.5 mg (31.8%) of indazole (**7b**), which were identical in all respects with those obtained previously, were isolated. TLC analysis of the reaction mixture showed the presence of ditolyl disulfide, ditolyl thiolsulfonate, and indazole (**6b**).

Thermolysis of 2-Acetyl-5-methyl-6-morpholino-3-pyrrolidino-1,4-benzoquinone Tosylhydrazone (2e). Formation of Ditolyl Disulfide, Ditolyl Thiolsulfonate, 2,3-Dihydro-6,9-dimethyl-7-morpholino-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (4e), 2,3-Dihydro-7-hydroxy-6,9-dimethyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (5a), and 3,6-Dimethyl-5-morpholino-4,7-dioxo-1*H*-indazole (7c)——40 mg of diaminoquinone tosylhydrazone (**2e**) was heated at 170° in an oil bath for a few minutes. Upon cooling, the reaction mixture was treated in the same way as described above. 8.6 mg (34.8%) of 7-morpholinopyrroloindole (**4e**), 1.6 mg (8.5%) of 7-hydroxypyrroloindole (**5a**), and 7.3 mg (33.9%) of indazole (**7c**) were isolated. TLC analysis of the reaction mixture showed the presence of ditolyl disulfide and ditolyl thiolsulfonate. **4e** showed the following characteristic properties. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1650 (C=O), 1615 (C=O), 1475, 1308, 1110, 963. Mass Spectrum *m/e*: 300 (M^+).

Acid-catalyzed Reaction of 2,3-Dihydro-6,9-dimethyl-7-morpholino-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (4e). Formation of 2,3-Dihydro-7-hydroxy-6,9-dimethyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (5a)——To a solution of 8 mg of 7-morpholinopyrroloindole (**4e**) in 1 ml of 1% hydrochloric acid and 0.5 ml of EtOH was added and the solution was stirred well for 2 hr at room temperature. A small amount of H_2O and 5 ml of $CHCl_3$ were then added and the organic layer was collected. It was dried and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel. 5 mg of 7-hydroxypyrroloindole, which was identical with that described previously, was obtained.

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